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Ariosa Diagnostics, Inc.

UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

SAN FRANCISCO DIVISION

ARIOSA DIAGNOSTICS, INC.,

Plaintiff,

vs.

SEQUENOM, INC.,

Defendant.

SEQUENOM, INC.,

Counterclaim Plaintiff,

vs.

ARIOSA DIAGNOSTICS, INC.,

Counterclaim Defendant,

and

ISIS INNOVATION LIMITED,

Nominal Counterclaim Defendant.

Case No. 3:11-cv-06391-SI

ARIOSA'S MOTION FOR SUMMARY JUDGMENT

Date of Hearing: September 20, 2013
Time of Hearing: 9:00 a.m.
Location: Courtroom 10
19th Floor
Judge: Hon. Susan Illston

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NOTICE OF MOTION AND MOTION

TO ALL PARTIES AND THEIR COUNSEL OF RECORD:

PLEASE TAKE NOTICE that on September 20, 2013, at 9:00 a.m., in the courtroom of the Honorable Susan Illston, 450 Golden Gate Avenue, San Francisco, California, Plaintiff and Counterclaim Defendant Ariosa Diagnostics, Inc. ("Ariosa") will, and hereby does, move for an order pursuant to Rule 56 of the Federal Rules of Civil Procedure for summary judgment on Sequenom, Inc.'s ("Sequenom") Counterclaim for Patent Infringement of United States Patent No. 6,258,540 (the "'540 patent") on the basis of Ariosa's Third Affirmative Defense (Invalidity), as set forth in Ariosa's Reply to Defendant and Counterclaim Plaintiff Sequenom's Answer and Counterclaims (Dkt. No. 52).

Ariosa requests that the Court enter summary judgment in favor of Ariosa on Sequenom's Counterclaim for Patent Infringement on the ground that the asserted claims of the '540 patent—claims 1, 2, 4, 5, 8, 19–22, 24, and 25—are invalid because they are not drawn to patent-eligible subject matter.

The Motion is based on the pleadings, the Memorandum of Points and Authorities following herein, the Declaration of David I. Gindler and corresponding exhibits, and the Proposed Order submitted herewith, and such other and further papers and argument as may be submitted to the Court in connection with the Motion.[1]

MEMORANDUM OF POINTS AND AUTHORITIES

I. PRELIMINARY STATEMENT

The '540 patent begins with the proclamation that it "has now been discovered that foetal DNA is detectable in maternal serum or plasma samples." (Ex. 1 at 1:50–51.) There can be no dispute that the applicants' claimed discovery—the presence of fetal DNA in maternal serum and plasma—is a natural phenomenon. Nor can there be any dispute that the discovery of a natural phenomenon is not patentable subject matter. Discoveries of natural phenomena have been excluded from patent protection for at least 150 years since the Supreme Court's decision in *Le*

[1] All citations in the form of "Ex. __" are to exhibits appended to the declaration of David I. Gindler submitted in support of this motion.

Roy v. Tatham, 55 U.S. (14 How.) 156 (1853). They are "part of the storehouse of knowledge of all men . . . free to all men and reserved exclusively to none." *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948).

The '540 patent is invalid because the applicants' *only* "invention" is their claimed discovery of this natural phenomenon. The applicants repeatedly stressed this very point—that the supposed novelty of their invention is the detection of fetal DNA in maternal serum or plasma—in their communications with the Patent Office. During prosecution of the '540 patent, they stated: "the ***key features*** of the claimed technique have been described in the Application, and, ***in particular, one skilled in the art is instructed to use maternal plasma or serum for the detection of foetal DNA***." (Ex. 2 at 7, emphasis added.) Similarly, during prosecution of the continuation application (which has the same specification as the '540 patent), they stated: "The instant application clearly teaches that large amounts of fetal nucleic acid are present in maternal serum or plasma . . . . ***The identification of such large amounts of fetal nucleic acid is, in itself, the solution to a significant technical problem, namely, how to obtain, non-invasively, analytically useful amounts of fetal nucleic acid for genetic analysis***." (Ex. 3 at 6, emphasis added.) Nothing in the specification or the prosecution history of the '540 patent identifies any point of novelty beyond this natural phenomenon.

In its most recent decision on the non-patentability of a natural phenomenon—*Association for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107 (2013)—the Supreme Court found that claims directed to the naturally occurring DNA sequence of genes responsible for increased risk of breast and ovarian cancer do not recite patent-eligible subject matter. *Id.* at 2111. Just as the discovery of these genes falls outside the scope of patentability, so too does the claimed discovery of fetal DNA in maternal plasma and serum. The genes in *Myriad* and the cell-free fetal DNA in this case are simply phenomena of nature. They cannot be patented.

The prohibition on patenting a natural phenomenon cannot be overcome through the artifice of grafting non-inventive activities onto that phenomenon—which is precisely what the applicants did when drafting the claims of the '540 patent. This longstanding rule was recently applied by the Supreme Court in *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*,

132 S. Ct. 1289 (2012). According to *Mayo*, a natural phenomenon does not become patentable merely by claiming "additional steps [that] consist of well-understood, routine, conventional activity already engaged in by the scientific community; and those steps, when viewed as a whole, add nothing significant beyond the sum of their parts taken separately." *Id.* at 1298.

The '540 patent does not pass muster under either *Mayo* or *Myriad*. The asserted claims merely combine a natural phenomenon—the presence of fetal nucleic acid in maternal serum and plasma—with "well-understood, routine, conventional activity already engaged in by the scientific community." The '540 patent does not disclose or claim anything new about techniques for detection of nucleic acids in serum or plasma. To the contrary, the patent instructs those skilled in the art to use well known techniques to detect fetal nucleic acids in maternal serum and plasma. Indeed, that is *exactly* how the applicants described their invention to the Patent Office in order to secure issuance of the '540 patent: "[I]t is not necessary for the Applicants to set out each of the many ways in which DNA might be analyzed. The description is sufficient simply by instructing one skilled in the art to carry out a suitable analysis. . . . [O]ne skilled in the art is readily able to apply the teachings of the present application to any one of the ***well known techniques for detection of DNA*** with a view to analysis of foetal DNA in [m]aternal plasma or serum." (Ex. 2 at 7–8, emphasis added.)

In short, even assuming the applicants were the first to discover the presence of fetal nucleic acid in maternal plasma and serum—and if the case proceeds, the record will show they were not—that is the *only* thing they discovered. By their own admission, the applicants employed well-understood, routine, conventional techniques to detect fetal nucleic acids in maternal serum and plasma. That is what they told the Patent Office to secure issuance of the '540 patent; Sequenom is bound by those admissions in this litigation. Because every asserted claim of the '540 patent amounts to no more than combining an unpatentable natural phenomenon with techniques that were well known before the date of the invention, they do not qualify as patent-eligible subject matter. Accordingly, all asserted claims are invalid and summary judgment should be entered for Ariosa.

II. ARGUMENT

A. Summary Judgment is Proper to Determine that the '540 Patent Does Not Cover Patent-Eligible Subject Matter

Summary judgment is appropriate when "there is no genuine dispute as to any material fact and the movant is entitled to judgment as a matter of law." Fed. R. Civ. P. 56(a). "[T]he burden on the moving party may be discharged by 'showing'—that is, pointing out to the district court—that there is an absence of evidence to support the nonmoving party's case." *Celotex Corp. v. Catrett*, 477 U.S. 317, 325 (1986). "[T]hen the burden shifts to the nonmoving party to set forth specific facts showing that there is a genuine issue for trial." *Shum v. Intel Corp.*, 633 F.3d 1067, 1076 (Fed. Cir. 2010).

Numerous cases have granted summary judgment of invalidity for failure to claim patent-eligible subject matter.[2] And so should this Court here. As discussed below, every fact upon which Ariosa relies in this motion is drawn from statements made by the applicants or on behalf of Sequenom: These statements come from (1) the '540 patent; (2) the prosecution history of the '540 patent; (3) the prosecution history of the continuation application; and (4) the declarations and deposition testimony of Sequenom's expert and percipient witnesses. There are thus no facts that Sequenom can genuinely contest. *See Constant v. Advanced Micro-Devices, Inc.*, 848 F.2d 1560, 1569–70 (Fed. Cir. 1988) (finding that statements in the specification and admissions during prosecution are binding on the patentee and affirming summary judgment of invalidity); *Del. Valley Floral Group, Inc. v. Shaw Rose Nets, LLC*, 597 F.3d 1374, 1382 (Fed. Cir. 2010) ("It is well settled that a court may disregard an affidavit submitted solely for the purpose of opposing a motion for summary judgment when that affidavit is directly contradicted by deposition testimony.") (internal quotation marks omitted). Ariosa is therefore entitled to summary judgment that the asserted claims are invalid.

[2] *E.g., Fort Props., Inc. v. Am. Master Lease LLC*, 671 F.3d 1317 (Fed. Cir. 2012); *CyberSource Corp. v. Retail Decisions, Inc.*, 654 F.3d 1366 (Fed. Cir. 2011); *SmartGene, Inc. v. Advanced Biological Labs., S.A.*, Civil Action No. 08–00642, 2012 U.S. Dist. LEXIS 44138 (D.D.C. March 30, 2012); *Bancorp Servs., L.L.C. v. Sun Life Assurance Co. of Can.*, 771 F. Supp. 2d 1054 (E.D. Mo. 2011).

B. Laws of Nature, Natural Phenomena, and Abstract Ideas are Not Patentable Subject Matter

"The obligation to determine what type of discovery is sought to be patented must precede the determination of whether that discovery is, in fact, new or obvious." *Parker v. Flook*, 437 U.S. 584, 593 (1978). The scope of patentable subject matter is set forth in Section 101 of the Patent Act, which states: "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor . . . ." 35 U.S.C. § 101.

The Supreme Court "has long held that this provision contains an important implicit exception. '[L]aws of nature, natural phenomena, and abstract ideas' are not patentable." *Mayo*, 132 S. Ct. at 1293 (quoting *Diamond v. Diehr*, 450 U.S. 175, 185 (1981)). "[E]ven though rewarding with patents those who discover new laws of nature and the like might well encourage their discovery, those laws and principles, considered generally, are 'the basic tools of scientific and technological work.'" *Mayo*, 132 S. Ct. at 1301 (quoting *Gottschalk v. Benson*, 409 U.S. 63, 67 (1972)). Thus, "[h]e who discovers a hitherto unknown phenomenon of nature has no claim to a monopoly of it which the law recognizes." *Funk Bros.*, 333 U.S. at 130.

Relying upon this rule, the Supreme Court has for many years found patents invalid that cover the discovery of a natural phenomenon. An early application of this rule can be found in *Funk Brothers*. There, the Supreme Court considered a patent that covered the discovery that certain naturally occurring bacteria strains could be mixed together to promote the growth of a variety of leguminous plants. The Supreme Court found the patent invalid because it reflected "no more than the discovery of some of the handiwork of nature . . . ." *Id.* at 131. In reaching this conclusion, the Supreme Court acknowledged that, "though [the discovery] may have been the product of skill, it certainly was not the product of invention. There is no way in which we could call it such unless we borrowed invention from the discovery of the natural principle itself." *Id.* at 132.

The Supreme Court has been vigilant in preventing patent applicants from evading this rule by simply dressing up non-patentable subject matter with other claim language that fails to recite

any inventive concept. This prohibition was made clear in *Parker v. Flook*, 437 U.S. 584 (1978). There, the Court considered a patent application that covered a method of updating "alarm limits," which reflected numerical measurements of certain operating conditions. The only novel feature of the claimed method was a mathematical formula for updating the alarm limits; all other elements reflected "conventional methods of changing alarm limits." *Id.* at 585–86. Relying on previous precedent holding "that the discovery of a novel and useful mathematical formula may not be patented," *id.* at 585, the Court concluded that the application did not cover patent-eligible subject matter, *id.* at 590. The Court reasoned that a "competent draftsman could attach some form of post-solution activity to almost any mathematical formula; the Pythagorean theorem would not have been patentable, or partially patentable, because a patent application contained a final step indicating that the formula, when solved, could be usefully applied to existing surveying techniques." *Id.* In language directly applicable here, the Court explained that the discovery of "a phenomenon of nature or mathematical formula . . . cannot support a patent *unless there is some other inventive concept in its application*." *Id*. at 594 (emphasis added).

The Supreme Court most recently applied this prohibition against patenting a natural phenomenon in *Association for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107 (2013). There, the Court found that Myriad's claims covering isolation of the BRCA1 and BRCA2 genes, whose presence in a mutated form significantly increases a woman's chances of developing breast and ovarian cancer, are not drawn to patent-eligible subject matter. The Court observed that "Myriad did not create or alter any of the genetic information encoded in the BRCA1 and BRCA2 genes. The location and order of the nucleotides existed in nature before Myriad found them. Nor did Myriad create or alter the genetic structure of DNA. Instead, Myriad's principal contribution was uncovering the precise location and genetic sequence of the BRCA1 and BRCA2 genes within chromosomes 17 and 13." *Id.* at 2116. Rejecting patent protection for this discovery, the Court reasoned that Myriad "found an important and useful gene, but separating that gene from its surrounding genetic material is not an act of invention." *Id.* at 2117. The Court emphasized that "the processes used by Myriad to isolate DNA were well understood by geneticists at the time of Myriad's patents . . . and are not at issue in this case." *Id.* at 2119–20. In contrast, the Court upheld

Myriad's claims directed to cDNA—laboratory synthesized, non-naturally occurring versions of the BRCA1 and BRCA2 genes that exclude those portions of the genes (called introns) that do not code for the expression of amino acids. *Id.* at 2119. The Court found that, unlike the act of isolating a naturally occurring gene, a "lab technician unquestionably creates something new when cDNA is made." *Id.*

C. A Natural Phenomenon Does Not Become Patentable by Combining It With Well-Understood, Routine or Conventional Activity

In *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S. Ct. 1289 (2012), the Supreme Court applied the principles that it previously articulated in cases such as *Funk Brothers* and *Flook*—and most recently affirmed in *Myriad*—to method claims centered around the use of a natural phenomenon. The Court held that the prohibition on patenting a natural phenomenon cannot be overcome by combining that phenomenon with additional steps that "consist of well-understood, routine, conventional activity already engaged in by the scientific community; and those steps, when viewed as a whole, add nothing significant beyond the sum of their parts taken separately." *Id.* at 1298. The Court ruled "that simply appending conventional steps, specified at a high level of generality, to laws of nature, natural phenomena, and abstract ideas cannot make those laws, phenomena, and ideas patentable." *Id.* at 1300. In reaching this conclusion, the Court explained that its prior precedents "insist that a process that focuses upon the use of a natural law also contain other elements or a combination of elements, sometimes referred to as an 'inventive concept,' sufficient to ensure that the patent in practice amounts to *significantly more* than a patent upon the natural law itself." *Id.* at 1294 (emphasis added).

In *Mayo*, the plaintiff challenged the validity of two patents relating to the proper dosage of thiopurine drugs in the treatment of autoimmune disorders. *Id.* at 1295. The patents covered "processes that help doctors who use thiopurine drugs to treat patients with autoimmune diseases determine whether a given dosage level is too low or too high. The claims purport to apply natural laws describing the relationships between the concentration in the blood of certain thiopurine metabolites and the likelihood that the drug dosage will be ineffective or induce harmful side-effects." *Id.* at 1294.

The Supreme Court held the patents were invalid. The Court began its analysis by observing that "Prometheus' patents set forth laws of nature—namely, relationships between concentrations of certain metabolites in the blood and the likelihood that a dosage of a thiopurine drug will prove ineffective or cause harm." *Id.* at 1296. The Court explained that "[w]hile it takes a human action (the administration of a thiopurine drug) to trigger a manifestation of this relation in a particular person, the relation itself exists in principle apart from any human action. The relation is a consequence of the ways in which thiopurine compounds are metabolized by the body—entirely natural processes." *Id.* at 1297. After defining the law of nature set forth in the patents, the Court then considered whether "the patent claims add *enough* . . . to allow the processes they describe to qualify as patent-eligible processes that *apply* natural laws . . . ." *Id.* (emphasis in original). The Court found that they did not. In particular, the Court found that determining the level of metabolites in the bloodstream "through whatever process the doctor or the laboratory wishes to use" requires no more than "well-understood, routine, conventional activity previously engaged in by scientists who work in the field." *Id.* at 1297–98.

As discussed below, all asserted claims of the '540 patent are invalid under the principles articulated in *Myriad*, *Mayo*, *Flook*, and *Funk Brothers*. The centerpiece of every asserted claim is a natural phenomenon: the presence of fetal nucleic acid in maternal serum and plasma. All other elements of the asserted claims recite well-understood, routine, conventional activity previously engaged in by scientists in the field. Accordingly, all of the asserted claims should be found invalid on the ground that they are not drawn to patent-eligible subject matter.

D. The Existence of Paternally Inherited Nucleic Acid in Maternal Plasma and Serum is a Natural Phenomenon

The '540 patent claims are based on the applicants' purported *discovery* of a *natural phenomenon*: the existence of paternally inherited nucleic acid of fetal origin in the plasma and serum of a pregnant woman. As the '540 patent itself states: "The most important *observation* in this study is the very high concentration of foetal DNA in maternal plasma and serum." (Ex. 1 at 16:12–14, emphasis added.) Sequenom's motion for a preliminary injunction reinforces this point: "Around 1996–1997, Drs. Dennis Lo and James Wainscoat, who had been working in the field of

prenatal diagnosis for many years, *discovered* that fetal DNA is *detectable* in maternal serum or plasma samples." (Ex. 7 at 4:18–20, emphasis added.)

There can be no dispute that the patent claims recite a natural phenomenon: Paternally inherited fetal nucleic acid is always, and has always been, present in the plasma and serum of a pregnant woman—just as the BRCA1 and BRCA2 genes "existed in nature before Myriad found them." *Myriad*, 133 S. Ct. at 2116. The presence of fetal nucleic acid in maternal plasma and serum is even more clearly a natural phenomenon than the correlations between metabolite levels and effective drug dosages discussed in *Mayo*, in that no human interaction (such as the administration of a drug) is required to trigger this natural phenomenon.

The self-proclaimed novelty of the '540 patent amounts to nothing more than an instruction to find this natural phenomenon—*i.e.*, to detect fetal nucleic acid in maternal plasma or serum. The applicants made this very point during prosecution of the '540 patent: "the ***key features*** of the claimed technique have been described in the Application, and, ***in particular, one skilled in the art is instructed to use maternal plasma or serum for the detection of foetal DNA***." (Ex. 2 at 7, emphasis added.) They reiterated this same point during prosecution of their continuation application: "The instant application clearly teaches that large amounts of fetal nucleic acid are present in maternal serum or plasma from the first trimester and can be detected. The identification of such large amounts of fetal nucleic acid is, ***in itself***, the solution to a significant technical problem, namely, how to obtain, non-invasively, analytically useful amounts of fetal nucleic acid for genetic analysis." (Ex. 3 at 6, emphasis added.) These admissions by the applicants are binding on Sequenom in this litigation. *Constant*, 848 F.2d at 1569–70.

As discussed below, there is nothing novel about the techniques that the applicants employed to detect this natural phenomenon. The asserted claims add nothing to this natural phenomenon beyond well-understood, routine, conventional activity undertaken by scientists in 1997, the priority date of the '540 patent.

E. The Asserted Claims Do Not Add Enough to the Natural Phenomenon to Qualify as Patent-Eligible Processes

In *Mayo*, the Supreme Court warned against "interpreting patent statutes in ways that make patent eligibility 'depend simply on the draftsman's art' without reference to the 'principles underlying the prohibition against patents for [natural laws].'" 132 S. Ct. at 1294 (quoting *Flook*, 437 U.S. at 593, brackets in original). To uphold any asserted claim of the '540 patent would ignore this warning and "risk disproportionately tying up the use of the underlying natural laws, inhibiting their use in the making of further discoveries." *Id.* As succinctly stated in *Mayo*, "the claimed processes (*apart from the natural laws themselves*) involve well-understood, routine, conventional activity previously engaged in by researchers in the field." *Id.* (emphasis added). All of the asserted claims are therefore invalid.

1. The Steps in Claim 1 Do Not Add Enough to Make the Claim Patentable

The core elements of the method covered by all asserted claims of the '540 patent can be found in claim 1: (1) "amplifying a paternally inherited nucleic acid from the serum or plasma sample"; and (2) "detecting the presence of a paternally inherited nucleic acid of fetal origin in the sample." Both of these steps reflect well-understood, routine, conventional activity as of 1997, the priority date of the '540 patent.

a. The "Amplifying" Step was Well-Understood, Routine, and Conventional

The first step of claim 1 is "amplifying a paternally inherited nucleic acid from the serum or plasma sample." This step—specified at a high level of generality (as in *Mayo*)—simply instructs those skilled in the art to amplify a paternally inherited nucleic acid from the serum or plasma sample through whatever process they wish to use.

It is undisputed that the "amplifying" step was well known by 1997. The '540 patent itself acknowledges that, "[a]n amplification of foetal DNA sequences in the sample is normally carried out. *Standard nucleic acid amplification systems can be used . . . .*" (Ex. 1 at 2:43–45, emphasis added.) Moreover, Sequenom itself has admitted that "[a] variety of ***common methods*** of

amplifying nucleic acids are referenced in the patent, including perhaps the most-widely used, polymerase chain reaction ('PCR')." (Ex. 7 at 8:25–27, emphasis added.)

Sequenom's expert also agrees that the amplification step was well known in 1997. He admitted in his declaration in support of Sequenom's motion for preliminary injunction that "***[v]arious methods of amplification were known*** back in 1997, but the most common is called the 'polymerase chain reaction,' or 'PCR,' which was invented in the 1980's." (Ex. 8 at ¶ 42, emphasis added.) When asked during his deposition "[h]ow would a person of skill in the art know in 1997 how you would, for example, amplify paternally inherited nucleic acids from the serum or plasma?," Dr. Evans replied that "[t]he technique of the polymerase chain reaction was already well known in science at that time as well as other methodologies which could be used. So it was known that if one had paternally derived nucleic acids of fetal origin, that one could amplify them, at least in principle." (Ex. 4 at 150:18–151:7.)

Even Dr. Lo agrees that the amplification step was well known. He stated in a declaration submitted during the prosecution of the continuation application that "[s]uitable amplification techniques can be ordinary PCR or more sophisticated developments thereof, *but these techniques were all known in the literature before the date of my invention.*" (Ex. 5 at ¶ 7, emphasis added.)

Nothing in the specification or the prosecution history suggests that the "amplification" step was inventive in any way—or that it was added to the claims as an unconventional approach to analyzing nucleic acid. Indeed, the amplification step was included in the claims of the '540 patent solely because *the examiner* required the applicants to make the amendment at the very end of prosecution. This is reflected in an Interview Summary memorializing a telephone call placed by the examiner after the applicants had already submitted an amendment (also required by the examiner) narrowing all claims to "paternally inherited" nucleic acid of fetal origin. The Interview Summary states: "The examiner called to discuss the after final amendment. While the applicants have provided the necessary changes, the examiner upon further consideration believes that an amplification step is a necessity for the claimed invention." (Ex. 9 at Interview Summary, Paper No. 14.) Thus, unless the Patent Office had required the applicants to make this further

amendment to secure issuance of the '540 patent, the applicants would have been content to obtain the patent without this limitation.

In short, there is unanimity among Sequenom, Dr. Lo, Dr. Evans, and the applicants that the "amplifying" step was well known by 1997. It adds nothing to transform the method of any asserted claim into patent-eligible subject matter.

b. The "Detecting" Step was Well-Understood, Routine, and Conventional

Like the "amplifying" step, the "detecting" step is specified at a high level of generality. This step simply instructs scientists who work in the field to find the natural phenomenon—paternally inherited fetal nucleic acids in maternal plasma or serum—through whatever process they wish to use. It is undisputed that DNA detection was well known by 1997.

The '540 patent specification gives examples of methods already used to detect other nucleic acids in serum or plasma: For example, by 1996, others had "demonstrated that tumour DNA can be detected by the polymerase chain reaction (PCR) in the plasma or serum . . . ." (Ex. 1 at 1:40–42.) Moreover, the applicants made numerous statements during the prosecution of the '540 patent that confirm the "detecting" step was well-understood, routine, and conventional as of 1997:

- "Although there are a wide variety of different types of polymorphisms [*i.e.*, nucleic acid sequence variations] which could be detected in connection with the present application, such polymorphisms and techniques for analysis of DNA ***are simply a matter of routine*** for one skilled in the art. Therefore, it is not necessary for the Applicants to set out each of the many ways in which DNA might be analyzed. The description is sufficient simply by instructing one skilled in the art to carry out a suitable analysis. . . . *[O]ne skilled in the art is readily able to apply the teachings of the present application to any one of the* ***well known techniques for detection*** *of DNA with a view to analysis of foetal DNA in [m]aternal plasma or serum.*" (Ex. 2 at 7–8, emphasis added.)

- "[T]he present invention results in the new identification that foetal DNA is present in maternal plasma or serum. Many of the points highlighted by the Examiner would be considered to be a matter of ***routine experimentation*** to one skilled in the art of DNA detection, to identify the most appropriate technique for a particular required diagnosis. The person skilled in the art has a ***broad range of techniques available for the detection*** of DNA in the sample." (*Id.* at 10, emphasis added.)
- "[O]ne skilled in the art is aware of a ***variety of techniques which might be used to detect different nucleic acid species***. For example, there are numerous techniques which might be used to detect repeat expansions, single gene mutations, deletions or translocations. ***These techniques are a matter of routine*** for one skilled in the art for the analysis of DNA." (*Id.* at 5, emphasis added.)
- "Improvement of the process or selection of the most appropriate of DNA analysis is simply a matter of ***routine experimentation*** which would be carried out by one skilled in the art based on the ***readily available techniques of DNA detection***." (*Id.* at 12, emphasis added.)

Dr. Lo, too, demonstrated his understanding that the "detecting" step was a conventional activity as of 1997 in the declaration he submitted in the prosecution of the continuation application:

- "[T]here is sufficient fetal DNA present in the maternal serum for ***detection by conventional PCR***. These detectable quantities of DNA could be utilised by those skilled in the art ***to detect any target sequence*** within the DNA, just by the use of the appropriate primer sequence in relation to that target." (Ex. 5 at ¶ 4(d), emphasis added.)
- "[I]t is credible to me that ***the method of the present invention***, using the ***known PCR techniques*** of restriction enzyme digest and 'ARMS', on maternal plasma or serum, ***would enable small genetic changes to be detected***. The present specification does not mention these techniques specifically, but I believe that any competent colleague in this field would appreciate that if simpler PCR techniques

> do not work well in relation to detecting any particular type of genetic deviation in fetal DNA in maternal serum or plasma, ***one would resort to the use of published more sophisticated techniques such as are described in this paper***." (*Id.* at ¶ 6(b), emphasis added.)

Sequenom's own witnesses also agree that the "detecting" step was conventional as of 1997. Dr. Dereck Tatman, Sequenom's Vice President of Business Development, admitted during his deposition that the '540 patent applicants "discovered the presence of . . . fetal nucleic acids in maternal circulation ***and the ability to detect those using standard technologies of the time***." (Ex. 6 at 36:2–5, emphasis added.) When Sequenom's expert Dr. Evans was asked during his deposition how a person of skill in the art would know of "the techniques for how to look for that [fetal] DNA" in maternal plasma, he replied that "[t]echniques such as the polymerase chain reaction were known in the field at that point," which could be used to detect fetal DNA. (Ex. 4 at 155:23–156:11.)

The undisputed, and overwhelming, evidence demonstrates that the "detecting" step was well-understood, routine, and conventional as of 1997. Accordingly, like the "amplifying" step, it cannot transform the claimed method into a patent-eligible use of a natural phenomenon.

2. The Steps in Claims 2, 4, 5, 8, 19–22, 24, and 25 Similarly Fail to Add Enough to Make these Claims Patentable

Claims 2, 4, 5, 8, 19–22, 24, and 25 include a few additional steps beyond amplification and detection of a paternally inherited nucleic acid in maternal plasma or serum. As discussed below, these additional steps—just like the "amplifying" and "detecting" steps—were well-understood, routine, conventional activities as of 1997. They do not transform any of these claims into patent-eligible subject matter.

a. The Limitations of Claims 2 and 4 Do Not Make these Claims Patentable

Claim 2 recites "[t]he method according to claim 1, wherein the foetal nucleic acid is amplified by the polymerase chain reaction." This claim does not add any steps to the method recited in claim 1. Instead, it limits the "amplifying" step in claim 1 to a particular method called

the polymerase chain reaction. The polymerase chain reaction, as Sequenom's expert admits, was invented in the 1980's, and was "the most common" method of amplification in 1997. (Ex. 8 at ¶ 42.) Accordingly, this additional limitation does not transform claim 2 into patent-eligible subject matter.

Claim 4 recites "[t]he method according to claim 1, wherein the foetal nucleic acid is detected by means of a sequence specific probe." The '540 patent specification repeatedly discloses that the "sequence specific probe" that the applicants used—the TaqMan system—was commercially available from Perkin-Elmer by 1997. (Ex. 1 at 6:36–7:10, 9:62–63, 10:5–7.) The applicants' use of a commercially available device for its intended purpose—detection of nucleic acid—reflects no inventive activity by the applicants.

b. The Limitations of Claims 5 and 8 Do Not Make these Claims Patentable

Claims 5 and 8 do not add any steps to the method of claim 1. Instead, they narrow the scope of the natural phenomenon covered by claim 1 into two mutually exclusive sub-classes, with each sub-class covered by one of the claims. Claim 5 recites "[t]he method according to claim 1, wherein the presence of a foetal nucleic acid sequence from the Y chromosome is detected." Claim 8 recites "[t]he method according to claim 1, wherein the presence of a foetal nucleic acid from a paternally-inherited non-Y chromosome is detected." These two sub-classes of paternally inherited nucleic acid—those found on the Y chromosome and those found on a non-Y chromosome—are just as much a natural phenomenon as the class within which they are subsumed: They describe a natural phenomenon present in the plasma and serum of pregnant women.

These limitations add nothing to transform the method of claim 1 into patent-eligible subject matter. Nucleic acid amplification and detection techniques are not chromosome specific—paternally inherited nucleic acid from the Y chromosome and from a non-Y chromosome can be amplified and detected using the same techniques. For example, one of the five studies described in the '540 patent specification is directed to determining whether a fetus possesses the RhD gene based on analysis of the plasma of a pregnant woman who lacks the RhD

gene. (*Id.* at 8:50–11:35.) The RhD gene is located on a non-Y chromosome (specifically, on chromosome 1). In the study, RhD gene sequences were amplified and detected by real time quantitative PCR analysis using devices and technologies that were commercially available from Perkin-Elmer. (*Id.* at 9:54–10:9, 6:36–7:67.) This same technique can also be used to detect Y chromosome sequences and was in fact used to detect paternally inherited nucleic acid from the Y chromosome in three of the five studies described in the '540 patent specification (Examples 2, 4, and 5). (*Id.* at 6:36–7:67, 12:25–26, 14:13–23.) There can be no dispute that amplification and detection techniques were well-understood, routine, and conventional in 1997—and could be applied to sequences on the Y chromosome or on a non-Y chromosome.

Moreover, Dr. Lo admitted that techniques known in the art could be used to target ***any*** fetal DNA sequence on any chromosome. In a declaration submitted during prosecution of the continuation application, Dr. Lo stated that "there is sufficient fetal DNA present in the maternal serum for detection by conventional PCR. These detectable quantities of DNA could be utilised by those skilled in the art to ***detect any target sequence within the DNA***, just by the use of the appropriate primer sequence in relation to that target." (Ex. 5 at ¶ 4(d), emphasis added.) The applicants also admitted during the prosecution of the '540 patent that "one skilled in the art is aware of a variety of techniques which might be used to detect ***different nucleic acid species***. For example, there are numerous techniques which might be used to detect repeat expansions, single gene mutations, deletions or translocations. ***These techniques are a matter of routine*** for one skilled in the art for the analysis of DNA." (Ex. 2 at 5, emphasis added.)

These admissions confirm that scientists who worked in the field in 1997 were already aware of a variety of techniques which could be used to amplify and detect a fetal nucleic acid from the Y chromosome or a paternally inherited non-Y chromosome. Because detecting a fetal nucleic acid from the Y chromosome or a non-Y chromosome was well-understood, routine, and conventional as of 1997, these steps do not transform claims 5 and 8 into patent-eligible subject matter.

c. The Limitations of Claims 19 and 20 Do Not Make these Claims Patentable

Claim 19 recites "[t]he method according to claim 1, wherein the sample contains foetal DNA at a fractional concentration of total DNA of at least about 0.14%, without subjecting it to a foetal DNA enrichment step." Claim 20 recites "[t]he method according to claim 19, wherein the fractional concentration of foetal DNA is at least about 0.39%." Because both fetal DNA and maternal DNA exist in maternal plasma and serum, fetal DNA naturally exists at a certain fractional concentration of total DNA. (Ex. 1 at 1:59–67.) The fractional concentration of fetal DNA to total DNA in a maternal serum or plasma sample without subjecting it to a fetal DNA enrichment step, *i.e.*, without subjecting it to a step that increases the naturally existing fractional concentration of fetal DNA, is itself a natural phenomenon.[3] Thus, these additional limitations cannot transform claims 19 and 20 into patent-eligible subject matter.

d. The Limitations of Claims 21 and 22 Do Not Make these Claims Patentable

Claims 21 and 22 introduce three additional steps: (1) "providing a maternal blood sample"; (2) "separating the sample into a cellular and a non-cellular fraction"; and (3) "providing a diagnosis based on the presence and/or quantity and/or sequence of the foetal nucleic acid." All of these steps recite activities that were well-understood, routine, and conventional by 1997.

(1) "Providing a Maternal Blood Sample" was Well-Understood, Routine, and Conventional

As the '540 patent acknowledges, blood samples from pregnant women were routinely collected by doctors long before 1997. (*See, e.g.*, Ex. 1 at 1:18–20.) ("More recently, techniques have been devised for predicting abnormalities in the foetus and possible complications in pregnancy, which use maternal blood or serum samples.") There is nothing in the '540 patent to suggest that "providing a maternal blood sample" as recited in claims 21 and 22 involves anything

[3] As Dr. Evans stated in his declaration, enrichment of a particular nucleic acid means increasing the relative copy number of that nucleic acid as compared to other nucleic acids. (Ex. 8 at ¶ 121.)

beyond well-understood, routine, conventional activity as of 1997.

(2) The "Separating" Step was Well-Understood, Routine, and Conventional

Claims 21 and 22 contain the step of "separating the sample into a cellular and a non-cellular fraction." A "cellular" fraction is a fraction of the blood sample that contains cells, and a "non-cellular" fraction is a fraction of the blood sample that does not contain cells. (Ex. 8 at ¶¶ 44, 96, 129.) Both plasma and serum are non-cellular fractions of a blood sample. (*Id.*) The '540 patent specification acknowledges that "[t]he preparation of serum or plasma from the maternal blood sample is carried out by ***standard techniques***." (Ex. 1 at 2:26–27, emphasis added.) Similarly, Dr. Evans testified that isolating maternal plasma was known prior to 1997. (Ex. 4 at 152:4–7.) Nothing in the '540 patent suggests that the "separating" step involves anything beyond "well-understood, routine, conventional activity already engaged in by the scientific community" as of 1997.

(3) "Providing a Diagnosis" is an Unpatentable Mental Process

Claims 21 and 22 include the step of "providing a diagnosis based on the presence and/or quantity and/or sequence of the foetal nucleic acid." This step—which involves no more than reporting what was detected by the claimed method—can be performed within the human mind. For example, when a doctor knows that RhD gene sequences are present in the plasma or serum of an RhD-negative mother, the doctor can provide a diagnosis of an RhD-positive fetus based on knowledge of RhD gene inheritance. It is well-settled that steps, such as providing a diagnosis, that "can be performed in the human mind, or by a human using a pen and paper," are unpatentable mental processes. *CyberSource Corp. v. Retail Decisions, Inc.*, 654 F.3d 1366, 1372 (Fed. Cir. 2011).

Sequenom may argue that claims 21 and 22 are valid because this step limits them to the field of prenatal diagnosis. This argument was rejected in *Flook*, which "stands for the proposition that the prohibition against patenting abstract ideas 'cannot be circumvented by attempting to limit the use of the formula to a particular technological environment . . . .'" *Bilski v. Kappos*, 130 S. Ct.

3218, 3230 (2010) (quoting *Diamond v. Diehr*, 450 U.S. 175, 191–92 (1981)). This reasoning extends to all exclusions from patentable subject matter, as evidenced by the Supreme Court's reliance on *Flook* in its *Mayo* decision, which concerned a law of nature rather than an abstract idea. Indeed, *Mayo* found that administering a thiopurine drug to a patient with an autoimmune disease was insufficient to create patent-eligible subject matter, even though the claim was limited to a particular technological environment (doctors who treat patients with certain diseases using thiopurine drugs). *Mayo*, 132 S. Ct. at 1297.

Moreover, this step involves no more than well-understood, routine, and conventional activity for scientists who worked in the field as of 1997. In reply to the enablement rejection in the first office action in the continuation application, the applicants admitted that "[t]he use of fetal nucleic acid analysis for a wide variety of ***diagnostic*** and other purposes is ***well known in the art***." (Ex. 3 at 6, emphasis added.) Dr. Lo confirmed that the "providing a diagnosis" step was routine as of 1997 in the declaration he submitted in support of the continuation application: "I believe . . . that when the competent person in the field has been taught, by the present invention, that the maternal plasma or serum contains sufficient fetal DNA in the high concentrations found, he ***would have no difficulty in carrying out fetal diagnosis*** to detect even small genetic defects . . . ." (Ex. 5 at ¶ 7, emphasis added.)

e. The Limitations of Claim 24 Do Not Make the Claim Patentable

Claim 24 contains the step of "removing all or substantially all nucleated and anucleated cell populations from the blood sample." Nucleated cells are cells that contain a nucleus, and anucleated cells are cells that do not contain a nucleus. (Ex. 8 at ¶ 135.) Removing all or substantially all nucleated and anucleated cell populations from a blood sample results in plasma or serum. (*Id.* at ¶¶ 44, 96, 135.) Thus, the analysis of the "separating" step in claims 21 and 22 applies equally to the "removing" step in claim 24—the step reflects purely conventional activity as of 1997.

f. The Limitations of Claim 25 Do Not Make the Claim Patentable

Claim 25 contains the step of "obtaining a non-cellular fraction of the blood sample." It makes no difference to the analysis as to whether this step is interpreted to include separating the

blood sample into a non-cellular fraction as well as receiving a non-cellular fraction that has already been prepared. Separating a blood sample into a cellular and non-cellular fraction was well-understood, routine, and conventional, as explained in the analysis of claims 21 and 22.

3. The Claimed Steps Viewed as a Whole Add Nothing Beyond the Sum of Their Parts

Sequenom will likely argue that the combination of routine steps in the asserted claims is somehow unconventional. Any such argument would be meritless. Indeed, Dr. Evans admitted that these steps were routinely performed together by 1997.

First, Dr. Evans testified that sample preparation (which includes both providing a blood sample and separating plasma and serum from the blood sample), amplification, and detection were steps that were commonly performed together before 1997. (Ex. 4 at 188:5–13.) ("Q: Others before Dr. Lo amplified and detected nucleic acids, right? A: Yes. Q: In fact, traditional DNA diagnostics well before 1997 traditionally involved three steps, right: Sample preparation, amplification, and detection, correct? A: Commonly.") Second, Dr. Evans testified that others before Dr. Lo amplified and detected nucleic acid in plasma and serum. (*Id.* at 188:15–17.) ("Q: [O]thers before Dr. Lo amplified and detected nucleic acid in plasma and serum, true? A: Yes.") Third, he admitted that "nucleic acids are usually amplified prior to sequencing," *i.e.*, detection. (Ex. 8 at ¶ 42.)

Moreover, the '540 patent specification acknowledges that amplifying and detecting fetal nucleic acid to provide a prenatal diagnosis were performed together prior to 1997 using DNA from intact fetal cells in maternal blood (as opposed to cell-free fetal nucleic acids, which are the subject of the '540 patent). (Ex. 1 at 1:31–35 ("WO 91/08304 describes prenatal genetic determination using foetal DNA obtained from foetal cells in the maternal blood. Considerable advances have been made in the enrichment and isolation of foetal cells for analysis . . . .").) Similarly, Dr. Evans admitted that in a non-invasive test using intact fetal cells in the maternal bloodstream predating the '540 patent invention, the fetal cells were isolated "and then subjected to polymerase chain reaction ('PCR') analysis and probing." (Ex. 8 at ¶ 40.)

Finally, the combination of claimed steps was routinely practiced by molecular biologists for detecting nucleic acid in related fields by 1997. This fact is made clear in the '540 patent specification, which states that "it has been demonstrated that tumour DNA can be detected by the polymerase chain reaction (PCR) in the plasma or serum of some patients (Chen et al 1996; Nawroz et al 1996)." (Ex. 1 at 1:40–43.) Thus, the isolation of plasma or serum from whole blood combined with the amplification and detection of nucleic acid by PCR was conventional and well-known by those skilled in the art, including the applicants themselves (who disclosed these examples in the '540 specification). The only difference between the cited examples and the '540 patent claims is the *source* of the cell-free DNA that is amplified and detected in plasma or serum; in each case, the source of the cell-free DNA is the result of a naturally occurring phenomenon.

Nor is there any magic to the additional limitation (in claims 21 and 22) of providing a diagnosis in combination with amplifying and detecting nucleic acid. The '540 patent specification acknowledges that the steps of amplifying and detecting nucleic acid in plasma or serum samples to provide a diagnosis were performed together for tumor DNA analysis by 1996. (Ex. 1 at 1:38–46 ("Recently, there has been interest in the use of plasma or serum-derived DNA for molecular diagnosis (Mulcahy et al 1996). . . . GB 2 299 166 describes non-invasive cancer diagnosis by detection of K-ras and N-ras gene mutations using PCR-based techniques.").)

Sequenom may repeat the argument that it advanced in support of its preliminary injunction motion: "The ability to detect cffDNA, rather than intact fetal cells, in maternal plasma through a fractionation/amplification/detection assay was not known ***at all***" in 1997. (Dkt. No. 114 at 8:27–9:1, emphasis in original.) By this statement, Sequenom appears to imply that the *techniques* used to "detect" cell-free DNA in maternal plasma were "not known at all" in 1997. This argument is directly contrary to the applicants' position during prosecution of the '540 patent: "[I]t is not necessary for the Applicants to set out each of the many ways in which DNA might be analyzed. The description is sufficient simply by instructing one skilled in the art to carry out a suitable analysis. . . . *[O]ne skilled in the art is readily able to apply the teachings of the present application to any one of the* ***well known techniques for detection*** *of DNA with a view to analysis of foetal DNA in [m]aternal plasma or serum."* (Ex. 2 at 7–8, emphasis added.)

When advancing this argument in support of its preliminary injunction motion, Sequenom referred to paragraphs 39–40 and 70–73 of Dr. Evans's original declaration. (Dkt. No. 114 at 9:1.) These paragraphs from Dr. Evans's declaration do not say or suggest that *the steps of the asserted claims—alone or in combination*—were anything other than routine and conventional activities in 1997. Rather, these paragraphs of Dr. Evans's declaration discuss that it was difficult for researchers to work with intact fetal cells isolated from maternal blood, and that it was unexpected to find cell-free fetal DNA in maternal plasma or serum (leading researchers to discard the plasma fraction of maternal blood before the applicants' discovery). (Ex. 8 at ¶¶ 39–40, 70–73.)

Dr. Evans's declaration simply reinforces that the only "invention" that the applicants purport to have discovered is the presence of cell-free fetal DNA in maternal plasma and serum. It makes no difference as to whether anyone had used "a fractionation/amplification/detection assay" with respect to cell-free fetal DNA in maternal plasma or serum before the applicants. There is no dispute that the steps of fractionation, amplification, and detection were well-understood, routine, conventional activities in 1997; applying these pre-solution activities to a newly discovered natural phenomenon does not create patent-eligible subject matter. That is the teaching of *Mayo*.

F. The Existence of Any Non-Infringing Alternatives to the Claimed Methods of the '540 Patent is Irrelevant to Whether the Claims Cover Patent-Eligible Subject Matter

Sequenom may argue (as it did in its reply in support of its preliminary injunction motion) that the '540 patent does not run afoul of *Mayo* because it does not tie up every conceivable way of detecting cell-free fetal DNA. (Dkt. No. 114 at 7:12–8:22.) For example, Dr. Evans claims that there are non-infringing alternatives to the methods claimed in the '540 patent—*i.e.*, "methods to detect cell-free fetal DNA without amplifying the DNA, and without separating maternal blood into a cellular and non-cellular fraction." (Ex. 10 at ¶ 25.)

This argument simply ignores the teaching of *Mayo*. It does not matter whether there are non-infringing alternatives to the methods claimed in the '540 patent for purposes of determining whether claims are drawn to patent-eligible subject matter. Rather, in *Mayo*, the Supreme Court reiterated its long-held view that a natural phenomenon is never patentable, and that it does not become patentable when combined with "well-understood, routine, conventional activity

previously engaged in by researchers in the field." *Mayo*, 132 S. Ct. at 1294. All asserted claims of the '540 patent combine the natural phenomenon of paternally inherited fetal nucleic acid with what, at most, can be described as conventional methods for amplifying and detecting nucleic acid. All of the claims are invalid for that reason. The Supreme Court's admonition against tying up "too much future use" of a natural phenomenon explains in part the *rationale* for its analysis of patent-eligible subject matter, but it does not make patentability depend on complete preemption of a natural phenomenon. *Id*. at 1302 ("The presence here of the basic underlying concern that these patents tie up too much future use of laws of nature simply reinforces our conclusion that the processes described in the patents are not patent-eligible, while eliminating any temptation to depart from case law precedent.").

It is thus irrelevant whether (as Dr. Evans suggests) there are methods of detecting paternally inherited fetal nucleic acid "that do[] not require amplification," (Ex. 10 at ¶ 26), or "that do[] not involve separation of the cellular and non-cellular components of maternal blood," (*id*. at ¶ 27).[4] Nothing in *Mayo* suggests that it would be permissible to patent a natural phenomenon combined with conventional activity already performed by the scientific community at the time of the invention, so long as there is at least some way of using the natural phenomenon not covered by the patented claim. *See Mayo*, 132 S. Ct. at 1294 (requiring an "inventive concept" rather than "well-understood, routine, conventional activity").[5] Rather, *Mayo* makes clear that combining a natural phenomenon with "well-understood, routine, conventional" activity would, if patentable, "tie up too much future use of laws of nature." *Id.* at 1302.

[4] Although Ariosa takes issue with the evidence that Dr. Evans relies upon to support these statements, it is unnecessary to rebut or otherwise address this evidence because it is simply irrelevant to the patentability analysis.

[5] It is disingenuous, to say the least, for Sequenom to suggest that it is possible to make use of the natural phenomenon that the applicants claim to have discovered with whole blood instead of with serum and plasma. The natural phenomenon that the applicants claim to have discovered is the presence of cell-free fetal DNA *in maternal serum and plasma*—the fraction of the blood from which the cells have been removed. Any method that makes use of whole blood would not be using the natural phenomenon at issue in this case.

III. CONCLUSION

The undisputed evidence leads to only one reasonable conclusion—the asserted claims are not drawn to patent-eligible subject matter. Accordingly, Ariosa respectfully requests that the Court grant summary judgment in Ariosa's favor on Sequenom's Counterclaim.

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